UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION I
475 ALLENDALE ROAD
KING OF PRUSSIA, PENNSYLVANIA 19406-1415

October 13, 2006

Docket No. 03014680 License No. 29-00117-06

Gregory R. Reinhard, DVM
Executive Director - Global Research Safety & Comp
Merck & Company, Inc.
Merck Research Laboratories
PO Box 2000, RY33-33-508
126 East Lincoln Ave
Rahway, New Jersey 07065

SUBJECT: INSPECTION REPORT 03014680/2005001, MERCK & COMPANY, INC., MERCK RESEARCH LABORATORIES, RAHWAY, NEW JERSEY

Dear Dr. Reinhard:

On September 21-22, 2005, Todd Jackson and Farrah Gaskins of this office conducted a safety inspection at the above address of activities authorized by the above listed NRC license. Mr. Jackson returned to the above address on March 3, 2006, for additional inspection activities. The inspection was limited to a review of radiation safety activities pertaining to use of iodine 125. Additional information provided in your correspondence dated November 9, 2005, and the telephone conversations on October 6 and November 7, 2005, as well as on March 10 and September 11, 2006, between Mr. Vincent Williams of your organization and this office were also examined as part of the inspection. The findings of the inspection were discussed with you and other members of your organization at the conclusion of the inspection. The enclosed report presents the results of this inspection.

Within the scope of this inspection, no violations were identified.

Current NRC regulations are included on the NRC's website at www.nrc.gov; select **Nuclear Materials; Medical, industrial, and academic uses of nuclear material;** then **toolkit index page.** The current NRC Enforcement Policy is included on the NRC's website at www.nrc.gov; select **What We Do, Enforcement,** then **Enforcement Policy.** Or you may obtain these documents by contacting the Government Printing Office (GPO) toll-free at 1-888-293-6498. The GPO is open from 7:00 a.m. to 9:00 p.m. EST, Monday through Friday (except Federal holidays).

No reply to this letter is required. Your cooperation with us is appreciated.

Sincerely,

Original signed by James P. Dwyer

James P. Dwyer, Chief
Commercial and R&D Branch
Division of Nuclear Materials Safety

Enclosure:
Inspection Report No. 03014680/2005001

cc:
Vincent P. Williams, Radiation Safety Officer
State of New Jersey

DOCUMENT NAME: E:\Filenet\ML062860377.wpd

SISP Review Complete: TJackson
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REGION I

INSPECTION REPORT

Inspection No.	03014680/2005001
Docket No.	03014680
License No.	29-00117-06
Licensee:	Merck & Company, Inc.
Address:	P.O. Box 2000 Rahway, NJ 07065-0900
Locations Inspected:	126 E. Lincoln Avenue, Rahway, New Jersey
Inspection Dates:	September 21-22, 2005, and March 3, 2006
Date Followup Information Received:	September 28 and 29, October 6, and November 7, 2005; March 10, 2006, and September 11, 2006
Exit Meeting Date:	September 13, 2006

Inspectors:

Original signed by — September 20, 2006

Todd J. Jackson, CHP — date
Senior Health Physicist

Original signed by — September 20, 2006

Farrah C. Gaskins — date
Health Physicist

Approved By:

Original signed by James P. Dwyer — ***September 20, 2006***

James P. Dwyer, Chief — date
Commercial and R&D Branch
Division of Nuclear Materials Safety

Document Name: E:\Filenet\ML062860377.wpd

EXECUTIVE SUMMARY

Merck and Company, Inc.
NRC Inspection Report No. 03014680/2005001

NRC conducted an unannounced onsite inspection of the Merck Research Laboratory (MRL) licensed program on September 21 and 22, 2005. The inspector conducted additional on-site inspection activities on March 3, 2006. The inspectors: (a) toured facilities where radioactive materials have been used; (b) examined the iodination hoods and boxes in laboratories 80W131B, 80-A31, and 80N1B-30; (c) examined the survey instruments and the thyroid bioassay instrumentation currently used in these laboratories as well as the instruments and facilities used between July 1997 and February 1999; (d) examined the areas previously used as laboratories for thyroid monitoring instruments, including rooms 80-B17 and 80-A23/B24; and (e) interviewed current staff. The inspectors also reviewed: (a) records of iodine-125 (I-125) labeled reagents ordered and received; (b) records of I-125 labeled reagents used and recorded by users on the iodination laboratory log sheets; (c) records of bioassay and dosimetry measurements for staff performing iodinations; (d) records of laboratory surveys; (e) records of dose assessments performed by the health physics staff; (f) records of annual hood flow measurements; (g) documentation of the MRL personnel monitoring policy and guidance for performing iodinations; (h) records of training; and (I) records related to the MRL permits authorizing use of I-125. Additional inspection-related information was also obtained by the NRC from MRL on September 28, September 29, October 6, and November 7, 2005, and on March 10 and September 11, 2006. No violations of regulatory requirements or safety concerns were identified.

REPORT DETAILS

I. Facilities and Equipment

a. Inspection Scope

Facilities and equipment used for personnel protection during radioiodinations were examined, including current facilities and those used since mid-1997. In the iodination labs the review covered the operation of, and selected test/maintenance records for, fume hoods, iodination boxes and associated exhaust fans. The inspection was conducted through personnel interviews, review of selected program records, and tours of facilities.

b. Observations and Findings

Inspectors toured the Merck & Company Research Laboratory (MRL) facilities, including laboratories 80W131B, 80-A31, and 80N1B-30 (an iodination lab in current use). The observed labs typically contained a fume hood, within which was a plexiglass iodination box (frequently referred to by licensee staff as a "glove box", used to contain radioiodine) enclosing a high pressure liquid chromatograph (HPLC). In laboratory 80W131B, the HPLC was situated on the bench top, inside an iodination box equipped with an exhaust fan to draw air flow into the box and through a charcoal filter before exhausting through a duct into the adjacent fume hood. A second iodination box, used for handling materials in preparation for HPLC injection, was located within the fume hood.

The inspector reviewed manufacturer's information describing the commercially available iodination boxes used by the licensee[1] and noted that the design incorporated open ports for hands to be inserted and open bases (the laboratory bench upon which the box is placed serves as the bottom of the box). The manufacturer's description of the box does not provide a means for attachment of gloves to the access ports, nor is there any reference to "glove box" in the description. The box design did not provide for sealed containment of contents, but instead provides an enclosure to collect volatile fumes and draw them away from the user and through the charcoal filter. The inspector determined that the inward air flow feature is important even for boxes installed inside fume hoods because the air flow into the fume hood is reduced in the face area occupied by the iodination box. The licensee stated that the expected fume hood face velocity was nominally 100 linear feet/minute, with the exhaust fan speed to be adjusted if the periodic check determined the fume hood was not performing as expected. MRL provided the following fume hood face velocity testing data collected December 11, 1997, December 10, 1998, and November 23, 1999.

[1]Model RM-1 Iodination Box, manufactured by Radiation Physics, Inc., 11809 Gordon Rd, Silver Spring, MD 20904

Fume Hood Flow Testing, Room 80W131B		
Test Date	"Actual Velocity" in linear feet/minute	Velocity in front of iodination box (linear ft/min)
December 11, 1997	85	47
December 10, 1998	99	57
November 23, 1999	112	84

Testing of fume hood face velocity determined in some cases that the “as-found” condition of the hood was less than the licensee’s specification of 100 linear ft/min, and flow was then adjusted to bring face velocity into specification. Data from measurements in front of the iodination boxes demonstrated the effect of the box within the hood, although data did not account for the additional inflow of room air through the box access ports.

Manufacturer information for the iodination boxes states that the 100 cubic feet per minute (cfm) fan blower draws air into the box through the two 5-inch front access portholes and through the charcoal filter before being exhausted. The system is designed to provide 150 linear feet/minute air flow without any interfering obstruction (such as worker arms reaching through the holes). The licensee did not measure or test air flow velocity into and through the iodination boxes. However, a researcher currently performing iodinations stated to the inspector that it is standard practice to verify air is flowing into the iodination box or fume hood prior to beginning iodinations.

c. Conclusions

No safety concerns or violations of NRC requirements were identified.

II. Material Receipt, Use, Transfer, and Control

a. Inspection Scope

The inspectors reviewed selected records of the handling and use of iodine-125 (I-125) for labeling of compounds used in MRL research. Inspection activities focused on the ordering, receipt, transfer and control of I-125 by the licensee.

b. Observations and Findings

The licensee practice for iodination of chemical compounds to be used in research included lab workers recording the quantity of I-125 used for each iodination procedure performed in a log maintained in the laboratory. The inspectors reviewed selected iodination logs completed during 1998 and 1999. Log records for 1997 no longer exist. Purchase orders of materials needed for one project specified 2 millicurie (mCi) quantities of I-125 labeled Bolton-Hunter reagent per vial. The logs recorded 4 mCi as used in the iodinations performed. Iodination procedures would therefore be expected to have necessitated the use of two 2 mCi vials of I-125 labeled reagent in the hood. Material receipt records demonstrate that when 2 mCi of I-125 labeled Bolton-Hunter reagent was ordered, the vials received from the manufacturer actually contained 3.0

mCi of I-125. The additional amount of I-125 was consistently included in the container received from the manufacturer, indicative of a standard practice designed to allow for radioactive decay and to assure the specific activity ordered was present when the product was later used.

The inspector contacted the manufacturer, who provided a vial label record from a batch of I-125 labeled Bolton-Hunter reagent as an example of labeling practices. Lot number BA12290 was assayed for "fresh lot" I-125 content on the date of shipment (December 28, 1998). The manufacturer specified the reagent was sufficiently stable during storage to be used for protein labeling at least three weeks after the "fresh lot date". The specified 2 mCi per vial activity was available as of the end of the three week shelf life and the vial label stated the package size was 2 mCi as of the calibration date of January 22, 1999. In order to deliver the stated 2 mCi vial activity on the calibration date, the manufacturer put 3.08 mCi I-125 into the package on the date of assay and shipment to its customer. Sufficient information was placed on the label to enable determination of I-125 activity in the vial on any date, accounting for radioactive decay.

For the project reviewed by the inspector it was the practice at MRL to use the labeled reagent within one to two days of receipt from the manufacturer. The dates of use logged for the labeled reagent indicated that many iodinations could have occurred with 5-6 mCi of I-125 total activity in vials on the lab bench (two vials, each with 3 mCi), rather than the 4 mCi recorded in the iodination logs. The inspectors did not identify any written instructions or procedures describing how the difference in logged vs. actual I-125 quantity was to be addressed administratively, nor was the licensee able to explain why the logged record of activity used differed from the receipt records. However, the information describing actual activity contained in the received vials was readily available to any user. Based upon receipt records documenting verification of shipment contents, the radiation safety office personnel were also aware of the actual activity in the vials: radioactive material received at MRL is processed by the radiation safety office staff prior to delivery to the lab researchers who ordered the material.

The inspectors reviewed selected external dosimetry records and verified that not all personnel performing iodinations were issued external dosimetry during the period of interest (July 1997-February 1999). Records for the first quarter 1999 were noted to include a vendor record stating a dosimeter had been issued to one worker and was subsequently returned to the vendor unused. The inspectors also reviewed an assessment performed by MRL, dated July 7, 1999, which demonstrated that no external monitoring was required because exposures did not approach the regulatory threshold at 10% of annual exposure limits. The inspectors verified calculations contained in the dose assessment, which estimated the external exposure per mCi of I-125 used. Using this information the inspectors independently verified that external exposure using 6 mCi per iodination, rather than the logged 4 mCi, would have resulted in a minor increase in the estimated external exposure and would still have produced external exposures that were less than the threshold at 10% of the regulatory limit to require monitoring.

Radioactive materials permit (RMP) #156, permitting some of the MRL iodinations, was reviewed by the inspectors. The permit specified that a urine sample was to be

submitted if a worker was using greater than 10 millicuries of I-125 per iodination procedure. Because the amount of I-125 used per iodination was less than 10 mCi, according to the iodination records reviewed, urinalysis need not have been provided for any of the iodinations reviewed. Records of personnel monitoring related to RMP #156 also showed that baseline thyroid bioassay measurements had been performed before individuals began performing iodinations and that the staff authorized to work under RMP #156 regularly complied with MRL procedures requiring thyroid bioassay in the days immediately following iodinations.

c. Conclusions

Iodination logs that recorded 4 mCi I-125 used per iodination (using two vials @ 2 mCi) may be inconsistent with receipt records documenting 3 mCi I-125 contained in each vial received. If this was the case, MRL policy states that external dosimetry should have been issued to personnel, and the policy was not followed. Although MRL policy was not followed, NRC regulations did not require the use of external dosimetry. The inspectors could not determine why the discrepancy between logged I-125 activities and received I-125 vial activities occurred. Regardless, the potential impact of these discrepancies on estimated radiation exposures was minor. MRL provided the inspectors with all requested information except for logs of iodinations performed in 1997. The inspectors noted that iodination logs are not specifically required to be retained by the regulations and the licensee stated the 1997 records had been destroyed in accordance with Merck record retention policy. The inspectors did not identify any safety concerns or violations of NRC regulations.

III. Training of Workers

a. Inspection Scope

Training provided to staff in preparation for performing iodinations was examined, as well as periodic refresher training.

b. Observations and Findings

Prior to initially using I-125 at MRL, Individuals who perform iodinations are required by the licensee to receive hands-on training under the supervision of the authorized user for a project (typically the Principle Investigator) utilizing the specific facilities, equipment and procedures the individual would use for the tasks to be performed. The inspectors reviewed records indicating which personnel had received what training during the period, as well as the current plan for initial and refresher training. Little detail was available regarding content of the training provided during the period 1997 - 1999. Through review of past program reviews, the inspectors noted that NRC inspections of the MRL iodination facilities conducted in April 1997, November 2001, and May-June 2003, identified no inadequacies in radiation safety training for laboratory personnel.

c. Conclusions

No safety concerns or violations were identified.

IV. Radiation Surveys and Bioassay

a. Inspection Scope

Radiation surveys examined included records of lab contamination surveys, room air monitoring, effluent monitoring, and bioassay measurements of personnel performing iodination activities. The inspectors also toured health physics labs and facilities containing radiation safety equipment and the thyroid monitoring instrumentation.

b. Observations and Findings

The inspectors reviewed selected examples of MRL dose assessments for individuals performing iodinations, including a May 4, 1999, external exposure history report and July 7, 1999, radiation dose assessment regarding a worker's external exposure while working at the facility. These reviews summarized and analyzed data collected routinely by the licensee during the 1997-1999 period. In the absence of external dosimetry, external exposure data was determined based on information provided by the worker, enabling realistic modeling of the radiation exposure involved with each aspect of routine iodinations performed. In May 1999, MRL made measurements of radiation levels present during iodination procedures, or calculated expected exposure rates where the rates were too low to be measured. The calculations were reviewed and verified by the inspectors, who concluded the dose assessments confirm the conclusion that MRL was not required by NRC regulations to monitor external radiation exposure for the cases examined because the annual exposures were less than 10% of the regulatory limit.

The inspectors determined that MRL performed thyroid dose assessments using a mathematical model that assumes the monitored individual has a normally functioning thyroid gland. A normally functioning thyroid accumulates iodine, making it easier to detect in the thyroid gland small intakes of I-125. Any I-125 activity measured in the thyroid can then be converted, using the dosimetric model, to estimate the activity intake and resulting radiation exposure to the thyroid gland. This method of thyroid monitoring is based upon the fundamental assumption that iodine is preferentially retained in the thyroid, using the relatively greater counts of radioactive decay emanating from the thyroid compared with the rest of the body. A background count is performed on the subject's thigh, considered to be representative of the body tissue general background. A test count is performed with the collimated detector pointed at the thyroid gland. The background count is subtracted from the thyroid count in order to obtain the net counts above background originating in the thyroid gland. The net difference in these counts is indicative of I-125 intake. If there is no accumulation of iodine in the non-functioning thyroid, the result of the thyroid monitoring will always determine zero net counts even if there was an intake. However, in this case, the non-stochastic thyroid organ dose limit (of 60 microCi annual limit on intake, or ALI) would no longer be the limiting exposure limit for the individual. If the concentration of iodine in the non-functioning thyroid tissue is the same as in the rest of the body, the stochastic whole body annual limit of 5 rem (200 microCi ALI) will be the applicable limiting dose.

The thyroid bioassay method used by MRL is described in peer-reviewed technical literature[2,3,4] and is commonly used and accepted throughout the United States. The inspectors reviewed the licensee's assessment dated July 7, 1999, which discussed the potential effects of thyroid function on thyroid monitoring and assigned dose. The MRL dosimetric model assumes each exposure is acute, that is, resulting from a single iodination procedure. Iodine retained in the thyroid is assumed to decay in accordance with a function based upon the technical literature. This model predicts that iodine in the thyroid reaches a peak about 5 days after intake and gradually declines thereafter. Each iodination exposure is modeled separately and measured radioactivity in the thyroid is used to determine thyroid dose. Subsequent thyroid measurements are corrected as necessary using the model to account for previously determined radioactivity in the organ, preventing overestimation of dose.

The inspectors noted that other methods of iodine exposure monitoring are feasible, such as breathing zone air samples collected during work. MRL does not perform breathing zone air sampling, and based upon the reviewed dose assessments and the expected exposures from work activities described there is no requirement that such sampling be performed. Additionally, breathing zone sampling does not account for absorption of iodine through the skin, another potential exposure pathway. Direct measurements of I-125 in the thyroid are acceptable as a method of monitoring exposure and assessing dose from all exposure pathways. NRC review of licensee bioassay records indicated that numerous licensee employees have been successfully performing, and continue to perform, safe iodination procedures with controlled exposures to radioactive I-125.

The inspectors examined methods used by MRL to calibrate and assure proper functioning of the thyroid monitoring radiation detection equipment. Records were reviewed for calibrations performed on July 19, 1997, January 16 and July 25, 1998, and July 13, 1999. Additionally, the inspector reviewed records of daily check source counts and daily background radiation counts. The licensee maintained a control chart for both parameters, plotting the daily counts over time. Acceptance criteria were established to clearly indicate when the counts were outside of the acceptable range, in which case the licensee's procedure was to declare the instrument inoperable and make necessary repairs or adjustments. The inspector noted that except for one 7 day period, control checks and background counts were within the licensee's acceptance criteria. During the period of July 1997 through December 1998 the detector was noted to be inoperable from November 1-8, 1998, due to "high voltage disabled", as annotated on the control chart. One thyroid count had been attempted during the period, was noted as being invalid by radiation safety staff, and was redone after the instrument was restored to

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[2] ICRP Publication 54, Individual Monitoring for Intakes of Radionuclides by Workers: Design and Interpretation.

[3] ICRP Publication 53, Radiation Dose to Patients from Radiopharmaceuticals.

[4] NCRP Publication No. 55, Protection of the Thyroid Gland in the Event of Releases of Radioiodine.

service. The licensee noted that the thyroid monitor location observed by the inspector had changed since the end of 1998. During the period July 1997 -February 1999 the monitor had been located in two different rooms, first in room 80-B17 and then in room 80-A23/B24. Additionally, new software had been installed in August 1998 which enabled individuals to perform monitoring counts of themselves. A representative of the radiation safety staff had performed the counts prior to August 1998.

c. Conclusions

Dose assessments reviewed by the inspectors demonstrated compliance with NRC regulations. Thyroid monitoring instruments and systems were properly calibrated and maintained. No safety concerns or violations of NRC requirements were identified.

V. Exit Meeting

An exit meeting was conducted by telephone on September 13, 2006, with the individuals identified in the attached list of licensee contacts.

PARTIAL LIST OF PERSONS CONTACTED

Licensee

V. Williams, Radiation Safety Officer *
G. Reinhard, Executive Director - Global Research Safety & Compliance
J. Miller, Corporate Radiation Safety Officer *
E. Wurtz, Director - Research, Environmental, Safety & Compliance *

* denotes participants in the exit meeting held on September 13, 2006